# Breaking Advances

1647 Highlights from Recent Cancer Literature

## Literature

### Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

### Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential
Stine F. Pedersen and Christian Stock

## Meeting Report

1658

### G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

### Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

## Priority Reports

1662

### Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients

**Précis:** Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

1668

### Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann

**Précis:** This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.

### Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response
David L. Masica and Rachel Karchin

**Précis:** New methods are offered to improve the identification of drug response biomarkers in cancer cells.

## Integrated Systems and Technologies

1689

### Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr

**Précis:** The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.

## Clinical Studies

1676

### Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response
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LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis

Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Ho, Georgina Lang, and Janine T. Erler

**Précis:** The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.

Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma


**Précis:** HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.

IFN-\(\gamma\)-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence

Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin

**Précis:** By helping resolve an inflammatory response, IFN-\(\gamma\) blockade can promote tumor regression by reprogramming the inflammatory microenvironment.

Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth

Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz

**Précis:** This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.

HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients

Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Mørch Frøsig, Stine Kiaer Larsen, Tobias Werenfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen

**Précis:** PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.
Dormant Cancer Cells Contribute to Residual Disease in a Model of Reversible Pancreatic Cancer


MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients
Xia Pu, Jack A. Roth, Michelle A.T. Hildebrandt, Yuanqing Ye, Hua Wei, John D. Minna, Scott M. Lippman, and Xifeng Wu

Precise: This large study of non-small cell lung cancer suggests that miRNA-related polymorphisms can predict clinical outcomes at a level that may be superior to other markers developed previously.

Proliferation-Independent Control of Tumor Glycolysis by PDGFR-Mediated AKT Activation
Cong Ran, Huan Liu, Yasuyuki Hitoshi, and Mark A. Israel

Precise: Findings argue that tyrosine kinase growth factor signaling directly affects glucose metabolism in glioma and is not a secondary response to enhanced proliferation, as suggested in other cancer models.

Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women
Eunjung Lee, David Van den Berg, Chris Hsu, Giske Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Anna H. Wu

Precise: Host genetic polymorphisms in a key growth factor in breast cancer may help identify women at an increased risk of breast cancer.

Telomere Length and Telomerase Activity Impact the UV Sensitivity Syndrome Xeroderma Pigmentosum C
Gerdine J. Stout and Maria A. Blasco

Precise: Findings reveal a role for the DNA repair protein XPC in telomere stability and how activation occurs for the ALT pathway of telomere maintenance, a broadly important aspect of tumor formation.

Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer
Sajjad Rafiq, William Tapper, Andrew Collins, Sofia Khan, Ioannis Politopoulos, Sue Gerty, Carl Blomqvist, Fergus J. Couch, Heli Nevanlinna, Jianjun Liu, and Diana Eccles

Precise: This study maps host genetic variations that affect risks of poor prognosis in early onset breast cancer patients, with implications for how aggressive treatments should be used to improve survival outcomes.

xCT Inhibition Depletes CD44v-Expressing Tumor Cells That Are Resistant to EGFR-Targeted Therapy in Head and Neck Squamous Cell Carcinoma
Momoko Yoshikawa, Kenji Tsuchihashi, Takatsugu Ishimoto, Toshifumi Yae, Takeshi Motohara, Eiji Sugihara, Nobuyuki Onishi, Takashi Masuko, Kunio Yoshizawa, Shuichi Kawashiri, Makio Mukai, Seiji Asoda, Hiromasa Kawana, Tanekii Nakagawa, Hideyuki Saya, and Osamu Nagano

Precise: Cells that express variant isoforms of the stem cell-determining factor CD44 rely on the activity of a cystine transporter subunit that affects redox status and EGFR function.

Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors
Ryan Alkins, Alison Burgess, Milan Ganguly, Gisèle Ursin, Woon-Puay Koh, Jian-Min Yuan, Daniel O. Stram, Mimi C. Yu, and Kullervo Hynynen

Precise: Noninvasive MBH-guided focused ultrasound allows targeted natural killer cells to circumvent the blood-brain barrier and treat HER2-amplified breast metastasis in the brain.

Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer
Salahaldin A. Tahir, Guang Yang, Alexei Goltssov, Ki-Duk Song, Chengzhen Ren, Jianxian Wang, Wenjun Chang, and Timothy C. Thompson

Precise: This study offers mechanistic insights into how aerobic glycolysis is increased in prostate cancer, possibly revealing critical targets for effective antimetabolic therapy in this setting.
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<tr>
<th>Page</th>
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<tr>
<td>1912</td>
<td>Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergistically Cooperates with Activated RAS Signaling in Driving Tumorigenesis</td>
<td>Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Vititell, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli</td>
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<td>1922</td>
<td>A Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation</td>
<td>Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Murali K. Ursam, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Said M. Sehti</td>
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<td>1934</td>
<td>Alkaline Phosphatase ALPPL-2 Is a Novel Pancreatic Carcinoma-Associated Protein</td>
<td>Pooja Dua, Hye Suk Kang, Seung-Mo Hong, Ming-Sound Tsao, Soyun Kim, and Dong-ki Lee</td>
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<td>1946</td>
<td>mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis</td>
<td>Liqun Zhao, Ping Yue, Faadio R. Khuri, and Shi-Yong Sun</td>
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<td>1993</td>
<td>Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity</td>
<td>Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhry, Hasan Alsaid, Beat M. Jucker, Jeffrey M. Axten, and Rakesh Kumar</td>
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<td>2003</td>
<td>Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer</td>
<td>Jordi Camps, Jason J. Pitt, Georg Emons, Amanda B. Hummon, Chanelle M. Case, Marian Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghadimi, Tim Beisbarth, Michael J. Dillipiantonio, Natasha J. Caplen, and Thomas Ried</td>
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ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.